

USE OF THE VINILOXYCARBONYL GROUP FOR AMINO PROTECTION IN PEPTIDE SYNTHESIS[†]

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In this communication we introduce a promising masking agent -- the vinyloxycarbonyl or VOC group -- for the protection of amino functions in peptide chemistry.

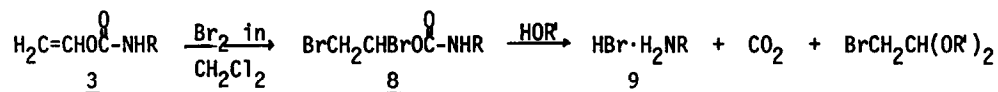
Amino acids are easily converted to their N-VOC derivatives (1) in dilute aqueous base using the known vinyl chloroformate¹ in dioxane as the acylating agent. The pH of the reaction medium is controlled (9-10) with a pH stat or by using an MgO suspension as the OH⁻ source, two procedures² widely utilized for the preparation of BOC and Z amino acids.³ Some of the VOC amino acids made are listed in Table I.⁴ Like BOC-AA's, the acids (1) are often oils but are easily characterized as the crystalline dicyclohexylammonium (DCHA) salts (2) from which 1 can be regenerated by extraction from carefully acidified solutions. Some VOC peptides (3) made

Table I. Representative N-VOC Amino Acids and Peptides⁴

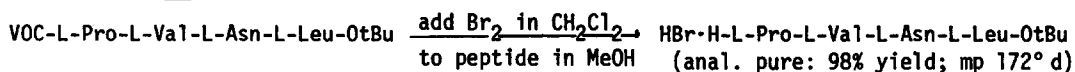
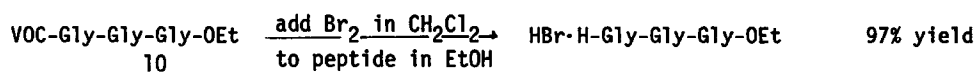
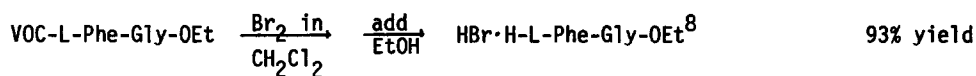
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|-------------------------|--------------|----------------------------------------|---------------|
| VOC-Gly-OH | mp 95-95.5° | VOC-Gly-Gly-OEt | mp 115-115.5° |
| VOC-L-Phe-OH | 56-58° | VOC-Gly-Gly-Gly-OEt | 173-175° |
| VOC-L-Ala-OH DCHA | 152.5-153° | VOC-L-Phe-Gly-OEt | 127.5-129° |
| VOC-L-Val-OH DCHA | 160-161.5° | VOC-L-Phe-L-Leu-OMe | 107.5-108.5° |
| VOC-L-Pro-OH | 93-94.5° | VOC-L-Asn-L-Leu-OMe | 167-168.5° |
| VOC-L-Asn-OH | 157.5-158.5° | VOC-L-Pro-Gly-OH DCHA | 157-160° |
| VOC-L-Hypro-OH DCHA | 179.5-181.5° | VOC-L-Glu(γOMe)-Gly-OEt | 88-89° |
| VOC-L-Glu(γOMe)-OH DCHA | 155-156° | VOC-L-Asn-Gly-Gly-OEt | 190.5-192° |
| VOC-L-Ser(O-tBu)-OH | 97-97.5° | VOC-L-Phe-L-Leu-O-Phenacyl | 151-152° |
| VOC-L-Lys(εBOC)-OtBu | 62-63.5° | VOC-L-Pro-L-Val-L-Asn-L-Leu-OtBu | 216° dec |
| VOC-L-Lys(εBOC)-OH DCHA | 152-154° | VOC-L-Ser(OtBu)-L-Phe-L-Leu-O-Phenacyl | 161-163° |

[†]This communication and the three closely related papers which follow are dedicated by the senior author to his mentor, Professor R. B. Woodward, on the occasion of his sixtieth birthday. Also acknowledged with special gratitude is Dr. Woodward's early encouragement of the research described here.

Deprotection by Bromination-Alcoholysis: Titration of the highly activated vinyl urethan group of simple VOC-peptides (3) with one equivalent of standardized Br₂ in CH₂Cl₂ to give the adduct (8) occurs so cleanly and rapidly that the process may be used as a quantitative assay for 3 - a fugitive yellow color appears at the end point.



Though unstable, 8 can sometimes be isolated, e.g. 8[R=H]: mp 122.5-123°, NMR: δ 3.98 [d,2], 5.2-6.2 [s,2], 6.77 [t,1], from VOC-NH₂ (mp 54.5-56.5°). The adducts (8) readily cleave to the desired HBr salts (9) when methanol or ethanol is added to the reaction mixture. Because of the increased susceptibility of 8 (vs. 4) to S_N1 substitution, it is often unnecessary to heat the mixture to complete the unblocking. Other VOC unmaskings by this method include:



Note the lack of complications from electrophilic aromatic substitution of phenylalanine, the successful use of a hydroxylic solvent during bromination, and the inertness of asparagine and the t-butyl ester unit. Only Trp, Tyr, Cys, and Met are likely candidates for side reactions with Br₂ under the experimental conditions. This procedure was tested partly in the hope that it would allow the use of the BOC group to mask secondary functions in peptide synthesis. Most agents now used for this purpose (benzyl, tosyl, etc.) are sometimes so stable they can only be detached under conditions in which the product peptide is itself partially dismembered. Two experiments confirm this hope. First, selective VOC removal from VOC-L-Lys(εBOC)-OtBu to give HBr·H-L-Lys(εBOC)-OtBu (mp 91-92.5°) was accomplished in 85% yield. In an even more sensitive test, (10) was cleaved in the presence of an equal amount of BOC-[1-¹⁴C]Gly-Gly-Gly-OEt. With 0.03 eq Bu₃N present to neutralize any strong acid impurity in the Br₂, the BOC peptide was reisolated and the HBr·H-Gly₃-OEt product contained only 0.4% of radioactive material.

Deprotection with Hg²⁺: In a last electrophile-induced⁹ scission, VOC-L-Phe-OH was unmasked with Hg(OAc)₂ in 9:1 HOAc-H₂O at 25° in 97±2% yield (isotope dilution assay). Since Hg²⁺ separation from small peptide esters is impractical, it is expected that this mild unblocking

